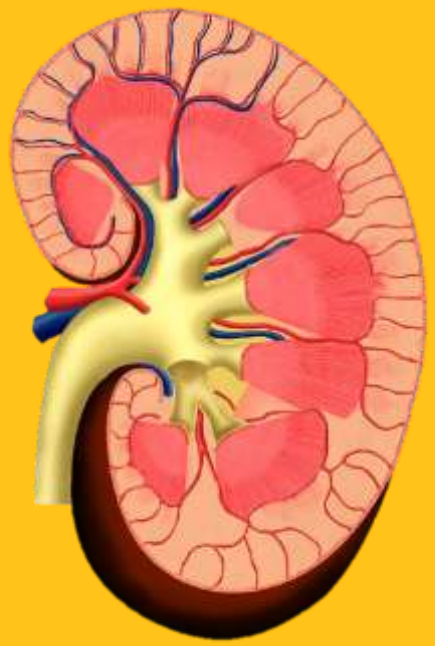
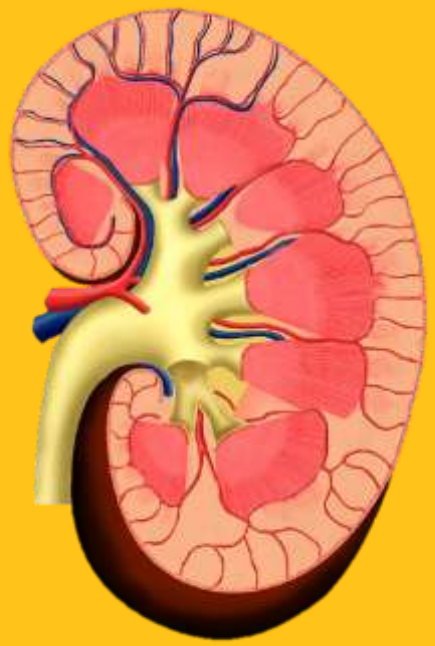
Hepatorenal syndrome



Professor Monir Bahgat

GRADE system

HRS



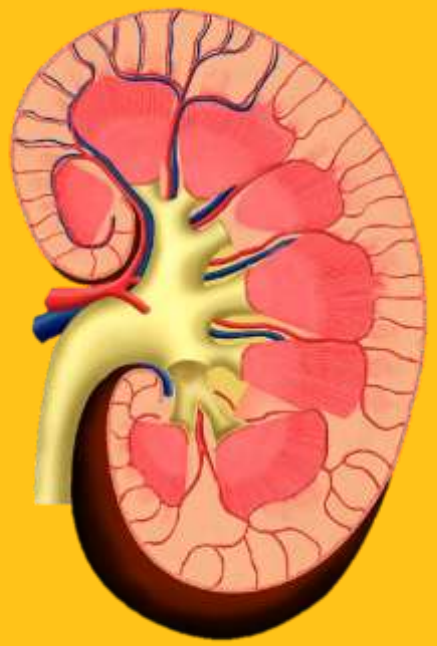
Professor Monir Bahgat

Grading evidence and recommendations (adapted from the GRADE system)

	Notes	Symbol
Quality of Evidence		
High	Large, high quality randomized control trials. We are confident that the true effect lies close to that of the estimate of the effect.	A
Moderate	Limited or conflicting data from randomized control trials. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	B
Low	Observational studies or very small randomized control trials. The true effect may be substantially different from the estimate of the effect.	C
Very low	Expert opinion. The estimate of effect is very uncertain, and often will be far from the truth.	D
Grading Recommendation[a]		
Strong 'We recommend'	Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful and effective	1
Weak 'We suggest'	Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment	2

Introduction

HRS



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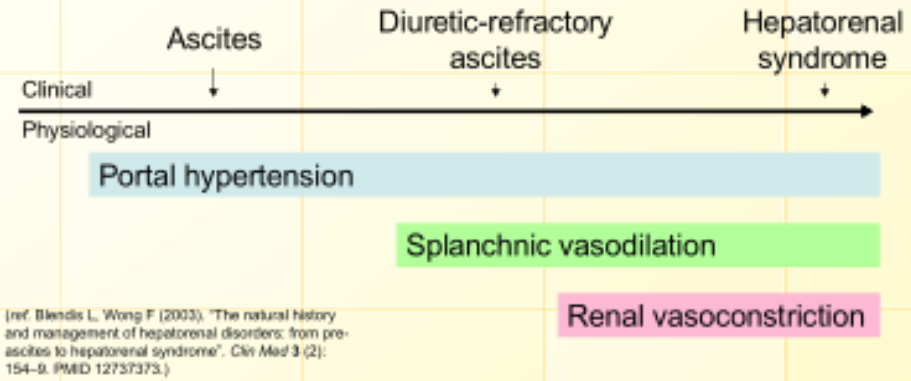
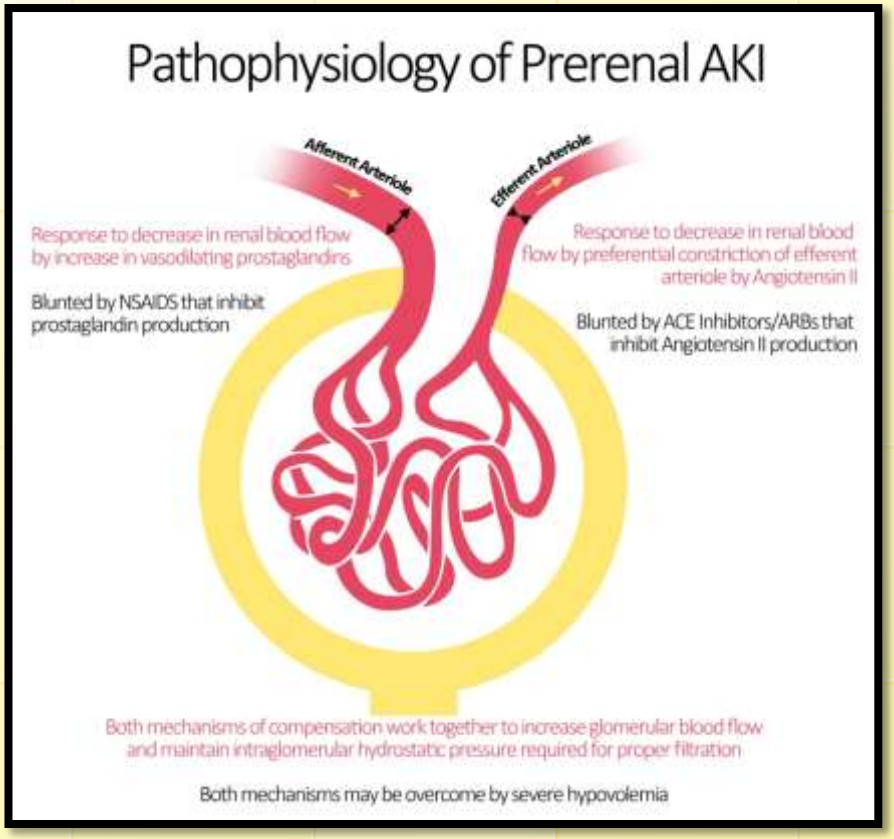
Definition

kidney injury resulting from renal vasoconstriction in the setting of systemic & splanchnic arterial vasodilatation in patients with advanced cirrhosis.



(ref. Blendis L, Wong F (2003). "The natural history and management of hepatorenal disorders: from pre-ascites to hepatorenal syndrome". *Clin Med* **3** (2): 154–9. PMID 12737373.)



Types

HRS is typically subdivided into two types:

- **Type-1:** Rapid deterioration in kidney function with the serum creatinine increasing by >100% from baseline to **>2.5 mg/dl** within a "**two-week"** period.

- **Type-2:** HRS occurs in patients with refractory ascites with either a steady but moderate degree of functional renal failure (≥ 1.5 mg/dl) or a deterioration in kidney function that does not fulfill the criteria for HRS type-1.

The 8th international consensus conference of the Acute Dialysis Quality Initiative (ADQI) Group

Nadim et al. Critical Care 2012, 16:R23

Occurrence

In patients with “advanced” cirrhosis, HRS occurs in:

18% within **one year** of diagnosis.

40% at **five** years.

The 8th international consensus conference of the Acute Dialysis Quality Initiative (ADQI) Group

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Prognosis

Untreated, “median survival” is:

Two weeks for patients with **type-1** HRS.

Four - six months in patients with **type-2** HRS.

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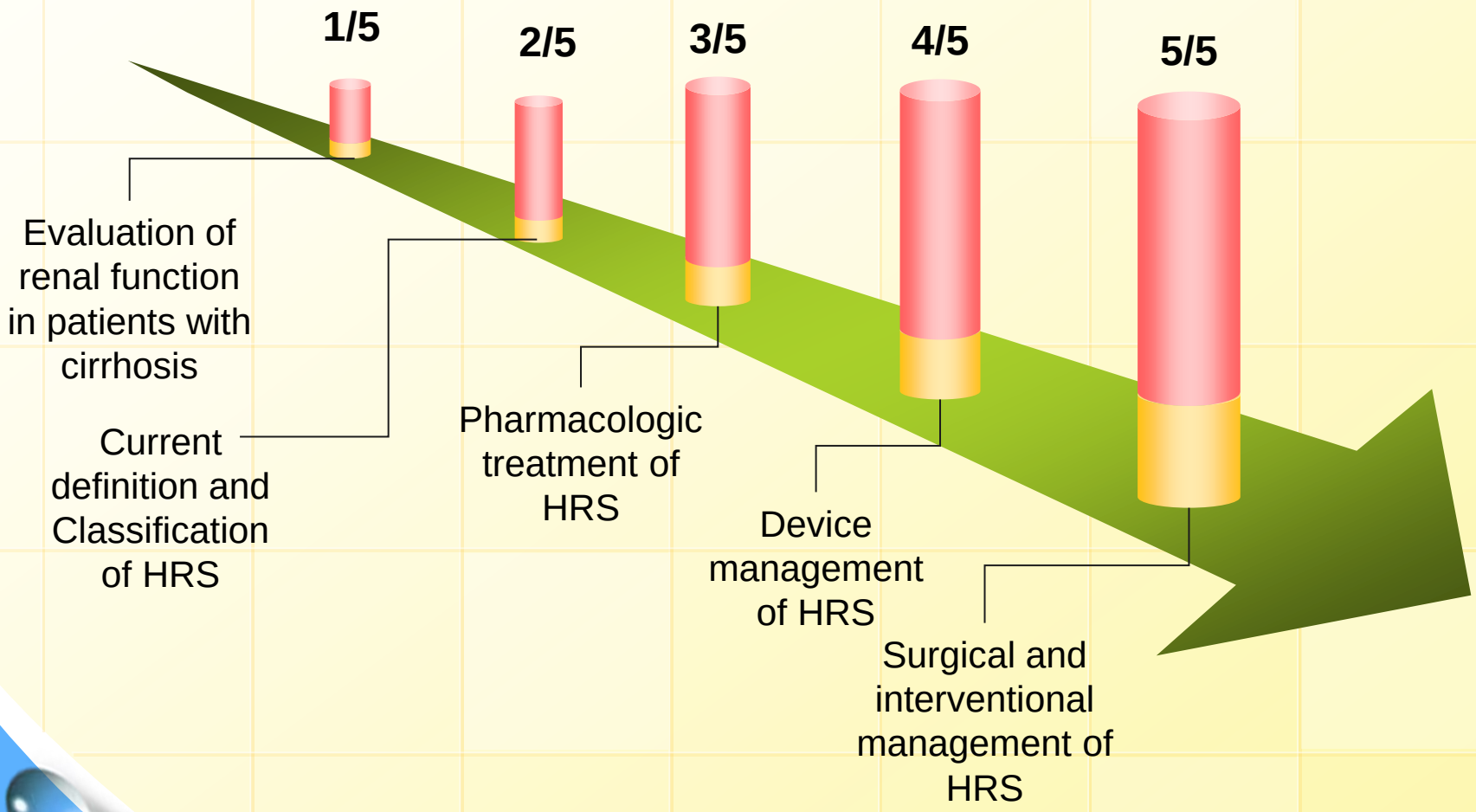
Agenda


1/5
2/5
3/5
4/5
5/5
Evaluation of renal function in patients with cirrhosis
Current definition and Classification of HRS
Pharmacologic treatment of HRS
Device management of HRS
Surgical and interventional management of HRS

I. Evaluation of renal function in patients with cirrhosis

1. Serum creatinine measurements should be used to evaluate renal function in patients with advanced cirrhosis until more reliable methods of measuring renal function become generally available (1D).

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Serum cystatin C ????

I. Evaluation of renal function in patients with cirrhosis

1. Serum creatinine measurements should be used to evaluate renal function in patients with advanced cirrhosis until more reliable methods of measuring renal function become generally available (1D).

exogenous clearance markers ???

I. Evaluation of renal function in patients with cirrhosis

2. GFR derived equations should be used cautiously for assessment of kidney function in cirrhosis since they tend to overestimate GFR (2D).

II. Definition and classification of renal impairment in cirrhosis

1. Classify AKI in the setting of cirrhosis according to RIFLE criteria (Not Graded).

Risk, **I**njury, **F**ailure, **L**oss, **E**ndstage

II. Definition and classification of renal impairment in cirrhosis

ADQI criteria for the definition and classification of AKI (modified RIFLE criteria)

AKI Stage	Serum creatinine criteria	Urine output criteria
1 (Risk)	Increase Scr ≥ 0.3 mg/dL within 48 hours or an increase 150 - 200% (1.5- to 2-fold) from baseline	< 0.5 ml/kg/hour for > 6 hours
2 (Injury)	Increase Scr 200% to 299% (≥ 2- to 3-fold) from baseline	< 0.5 ml/kg/hour for > 12 hours
3 (Failure)	Increase Scr ≥ 300% (≥ 3-fold) from baseline or Scr ≥ 4.0 mg/dL with an acute increase of ≥ 0.5 mg/dL or initiation of renal replacement therapy	< 0.3 ml/kg/hour for 24 hours or anuria for 12 hours

II. Definition and classification of renal impairment in cirrhosis

1996 Criteria

Major Criteria

- Chronic or acute liver disease with advanced hepatic failure and portal hypertension.
- Serum creatinine > 1.5 mg/dL or 24-h creatinine clearance of < 40 mL/min.
- Absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs. Absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhea) or renal fluid losses
- No sustained improvement in renal function defined as a decrease in serum creatinine to < 1.5 mg/dL or increase in creatinine clearance to 40 mL/min or more following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline.
- Proteinuria < 500 mg/dL and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.

Minor Criteria

- Urine volume < 500 mL/d
- Urine sodium < 10 mEq/L
- Urine osmolality > plasma osmolality
- Urine red blood cells < 50 per high power field

2007 Criteria

- Cirrhosis with ascites
- Serum creatinine > 1.5 mg/dL
- No improvement of serum creatinine (decrease to a level ≤ 1.5 mg/dL) after at least two days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/day, microhematuria (> 50 red blood cells per high power field), and/or abnormal renal ultrasonography

II. Definition and classification of renal impairment in cirrhosis

2. Classify CKD in the setting of cirrhosis according to Kidney Disease Outcomes Quality Initiatives (K/DOQI) (Not Graded).

II. Definition and classification of renal impairment in cirrhosis

3. Acute on CKD in cirrhosis is defined as a rise in SCr ≥ 0.3 mg/dL in <48 hours or an increase in SCr ≥ 50% from baseline, or in a patient with cirrhosis whose baseline GFR has been <60 ml/min calculated with the MDRD-6 formula for >3 months (Not Graded).

II. Definition and classification of renal impairment in cirrhosis

Diagnosis	Definition
Acute Kidney Injury	• A rise in Scr ≥ 50% from baseline, or a rise Scr > 0.3 mg/dL • Type-1 HRS is a specific form of acute kidney injury
Chronic Kidney Disease	• GFR < 60 ml/min for > 3 month calculated using MDRD-6 formula
Acute on Chronic Kidney Disease	• Rise in Scr ≥ 50% from baseline or a rise of Scr > 0.3 mg/dL in a patient with cirrhosis whose GFR is < 60 ml/min for > 3 month calculated using MDRD-6 formula

III. Pharmacologic treatment of HRS

1. We suggest using hemodynamic monitoring, when possible, to help with the management of fluid balance in patients with HRS (2D).

III. Pharmacologic treatment of HRS

2. We recommend that patients with type-1 HRS be optimally resuscitated with albumin (initially 1 g of albumin/kg for two days, up to a maximum of 100 g/day, followed by 20 to 40 g/day) in combination with a vasoconstrictor (1A), preferentially terlipressin (2C).

III. Pharmacologic treatment of HRS

Drug	Dose
Terlipressin	0.5 to 2.0 mg intravenously every 4 to 6 hours; with stepwise dose increments every few days if there is no improvement in serum creatinine, up to a maximum dose of 12 mg/day as long as there are no side effects. Maximal treatment 14 days
Vasopressin	0.01 U/min to 0.8 U/min (continuous infusion). Titrate to achieve a 10 mm Hg increase in MAP from baseline or MAP > 70 mmHg
Noradrenaline	0.5 to 3.0 mg/hour (continuous infusion). Titrate to achieve a 10 mmHg increase in MAP
Midodrine + Octreotide	Midodrine: 7.5 to 12.5 mg orally three times. Titrate to achieve a 15 mm Hg increase in MAP from baseline Octreotide:100 to 200 µg subcutaneously three times daily or 25 µg bolus, followed by intravenous infusion of 25 µg/hour

III. Pharmacologic treatment of HRS

Parikh and Moitra *Critical Care* 2012, **16**:421
http://ccforum.com/content/16/2/421

CRITICAL CARE

LETTER

Hepatorenal syndrome: one size does not fit all

Amay Parikh[1]* and Vivek K Moitra[2]

III. Pharmacologic treatment of HRS

We read with interest the Acute Dialysis Quality Initiative (ADQI) VIII consensus statements on the treatment of patients with hepatorenal syndrome (HRS) and acute kidney injury [1]. While we appreciate the authors' discussion, we question the hemodynamic recommendations and suggest further areas of study (Section III in [1]).

Renal perfusion relies upon cardiac output, renal blood flow, and autoregulation. HRS influences cardiac output and systemic vascular resistance, and establishing a pressure gradient across the glomerulus ensures renal blood flow and glomerular filtration rate [2,3]. In fluid responsive patients, volume resuscitation is a key component of HRS management.

The traditional target mean arterial pressure (MAP) of 65 mmHg to ensure renal perfusion assumes that 'one size fits all' in HRS. The kidneys are in the abdominal compartment, and intraabdominal pressure varies among individuals. The pressure of the compartment during disease states that cause ascites decreases renal perfusion pressure and should be overcome, especially when autoregulation is impaired [4]. In other words, the arbitrary suggestion of increasing the MAP by 10 mmHg (Table 6 in [1]) may not be enough (or may be too much).

Titrating norepinephrine to a baseline MAP of 65 mmHg plus the intraabdominal pressure [4] and administering terlipressin or vasopressin (which may constrict the efferent glomerular arteriole [5]) may be an effective hemodynamic strategy to ensure renal perfusion pressure. Although this recommendation may not be based on grade A evidence, it is physiologically sound (establishes a pressure gradient) and may inspire further studies of hemodynamic management in patients with HRS.

III. Pharmacologic treatment of HRS

Authors' response

Andrew Davenport, Mitra K Nadim and John A Kellum, for the authors

We thank Drs Parikh and Moitra for their letter concerning our paper reviewing the medical management of HRS [1]. We agree that the hemodynamic alterations of advanced liver disease are complex. Early in the course of cirrhosis the effects of increased splanchnic vasodilatation, primarily due to local nitric oxide synthesis, have limited systemic manifestations. As liver disease progresses, however, systemic vasodilatation develops despite increased visceral sympathetic tone, renin-angiotensin-aldosterone activation, endothelin and vasopressin release, leading to a loss of renal auto-regulation [6], increasing the risk of 'pre-renal' acute kidney injury [7].

Terlipressin, a potent vasoconstrictor, particularly for the mesenteric circulation, increases renal perfusion pressure. However, the optimum renal perfusion pressure for patients with cirrhosis is unknown [1]. Following coronary artery surgery, renal auto-regulation is impaired and glomerular filtration rates are higher, with a mean arterial pressure of 70 mmHg [8]. Patients with cirrhosis differ in that they may have ascites and right atrial dilatation. Studies in patients with heart failure with elevated right atrial pressures have shown that intra-abdominal pressures even as low as 8 mmHg adversely affect renal function [9]. In patients with cirrhosis, ascitic drainage can be shown to have an almost immediate dynamic effect on renal perfusion, with changes in intra-renal pressure demonstrated with color Doppler assessment of intra-renal blood flow. Further prospective studies are thus required to determine whether there is an optimal target renal perfusion pressure for patients with HRS treated with terlipressin, but these will also need to include assessment of intraabdominal pressure.

IV. Device management of HRS

1. We recommend withholding renal replacement therapy (RRT) in patients with decompensation of cirrhosis who are not candidates for liver transplantation (1D).

IV. Device management of HRS

2. We suggest that **“artificial liver support therapies”** for HRS be limited to research protocols (2D).

IV. Device management of HRS

	Technique
Artificial (Non-cell based)	
Hemoperfusion	Removal of protein-bound toxins by circulating blood over a sorbent material
Hemodiabsorption	Hybrid process in which blood is passed through a hemodialyzer containing a suspension of sorbent material, such as charcoal or resin, in the extracapillary space
Plasma Exchange	Exchange of plasma volume
Plasmapheresis	Plasma is separated from the cellular blood components and replaced with normal plasma constituents, allowing the removal of circulating toxins and waste products.
Plasma Filtration	Removes a specific plasma fraction containing substances within a specific molecular weight.
Albumin dialysis	Albumin containing dialysate using an anion exchange resin and active charcoal adsorption allowing albumin-bound toxins in the blood to cross the membrane and bind to the albumin. Water soluble toxins are dialyzed from the albumin circuit by a standard hemodialysis or continuous renal replacement therapy (CRRT) machine.
• Single Pass Albumin Dialysis (SPAD)	
• Prometheus	
• Molecular Adsorbent Recirculating System (MARS)	
Bioartificial (Cell-based)	
Porcine	
• HepatAssist • Bioartificial Liver Support System (BLSS) • Modular Extracorporeal Liver Support (MELS) • Hybrid-Bioartificial Liver (HBAL) • Radial Flow Bioreactor (RFB) • TECA-Hybrid Artificial Liver Support System • AMC-Bioartificial Liver	
Human	
• Extracorporeal Liver Assist Device (ELAD)	

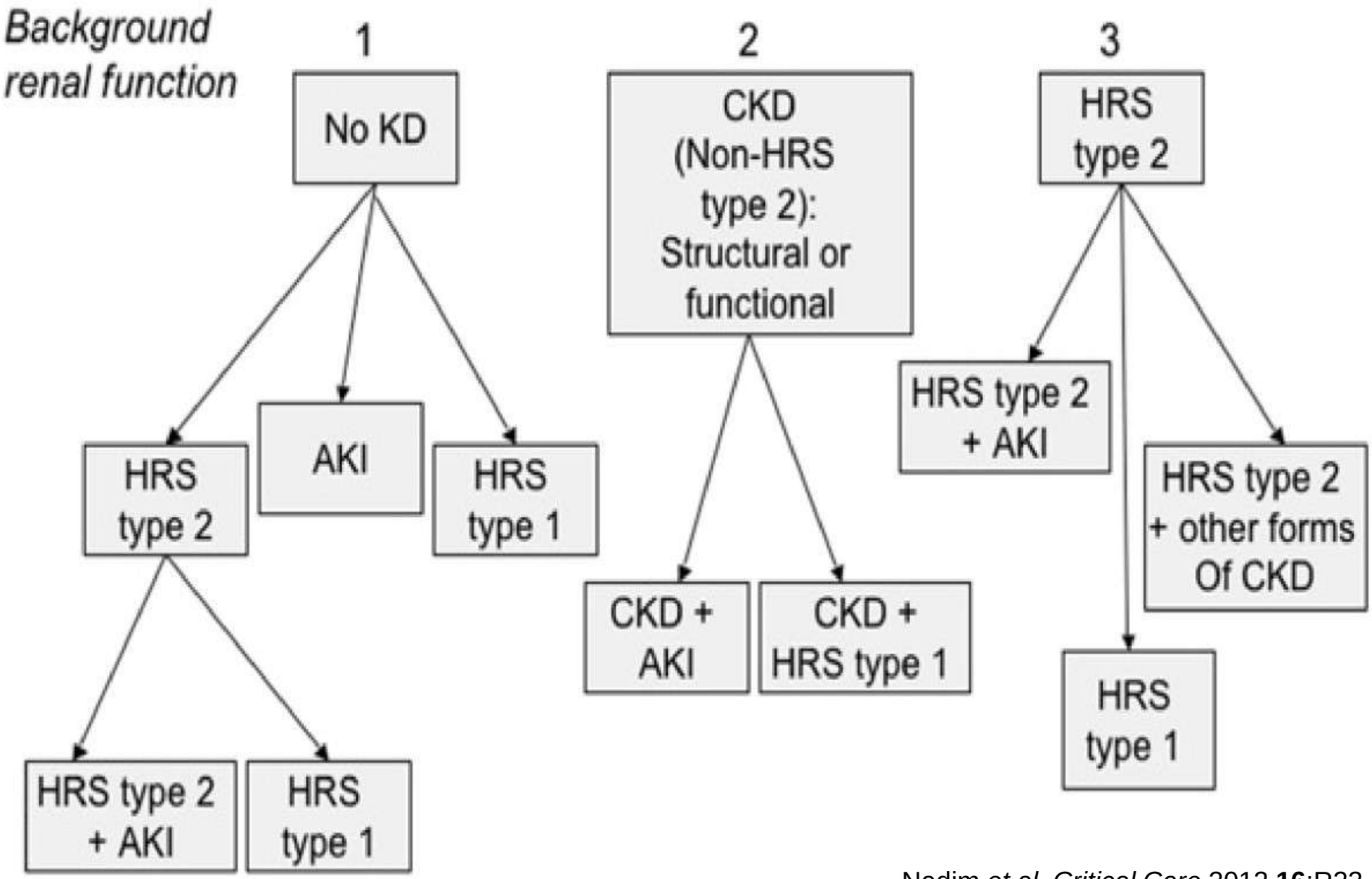
V. Interventional & Surgical management of HRS

1. We recommend use of a transjugular intrahepatic portosystemic shunt (TIPS) as a treatment option for patients with type-2 HRS with refractory ascites who require large volume paracentesis (1C).

V. Interventional & Surgical management of HRS

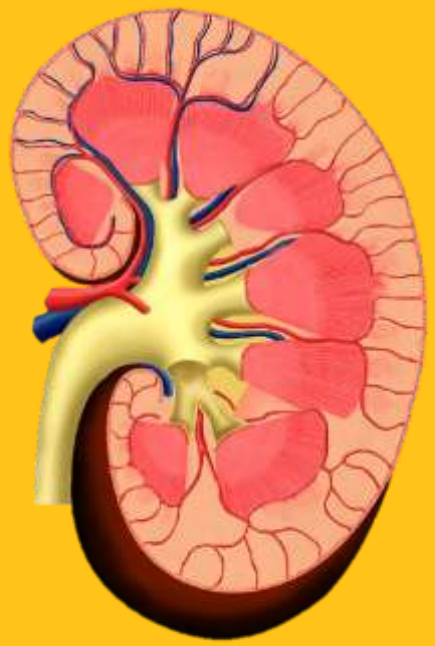
2. We suggest liver transplantation alone for candidates with type-1 HRS for less than four weeks and simultaneous liver kidney (SLK) for those at risk for non-recovery of renal function (2D).

Spectrum of Hepatorenal Disease in Patients with Advanced Cirrhosis



Nadim *et al. Critical Care* 2012 **16**:R23

Thank You!



Professor Monir Bahgat

DIAEGYPT, 2012